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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

18M1/0320

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ART UNIT	PAPER NUMBER
1806	24

DATE MAILED: 03/20/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

Docketed: 6-20-97

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 12/12/96

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 30-33 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 30-33 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1806.

2. Applicant's amendment, filed 12/12/96 (Paper No. 23), is acknowledged.
Claims 30, 32-33 have been amended

Claims 30-33 are pending and being acted upon presently.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.
This Action will be in response to applicant's arguments, filed 12/12/96 (Paper No. 23), The rejections of record can be found in the previous Office Action (Paper No. 21).

4. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

5. Claims 30-33 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed: "a method of interfering with interaction between a bone marrow stromal cells expressing VCAM-1 and a hemopoietic precursor cell which comprises administering an antibody to VCAM-1 in an amount effective to decrease VCAM-1-mediated adhesion between the bone marrow stromal cell and hemopoietic precursor cell".

Applicant 's amendment, filed 12/12/96 (Paper No. 23), has directed support for the amended claims to (1) page 4, lines 11-16; however said passage refers to blocking lymphocyte binding to activated bone marrow stromal cells and not hemopoietic precursors; (2) page 14, lines 28-32 which similarly refers to blocking lymphocyte adhesion and not hemopoietic precursors; and (3) page 17, lines 24-33 which refers to the expression of VLA-4 on human CD34+ bone marrow cells and infer that VCAM-1-VLA-4 interactions occur between hemopoietic cells and stromal elements and go on further to disclose the use of VCAM-1-specific antibodies to prevent GVHD.

There does not appear to be support for interfering with hemopoietic cell-stromal cell interactions with VCAM-1-specific antibodies nor is there support how the skilled artisan would use such procedures. The inhibition of adhesion mediated by VCAM-1-specific antibodies as disclosed in the specification as filed is directed towards inhibiting lymphocyte adhesion such as useful in inhibiting GVHD and not towards inhibiting hemopoietic stem and/or progenitor cell adhesion.

Applicant's amendment in conjunction with the Torok-Storb declaration under 37 C.F.R. § 1.132, filed 12/12/96 (Paper No. 23), have been fully considered but are not found convincing. Torok-Storb states that one of ordinary skill in the art after being informed of the discovery of VCAM-1 expression on bone marrow stromal cells and their involvement in mediating adhesive interactions between hemopoietic cells and stromal elements would have understood from the disclosure in the application that a clear therapeutic benefit of administering VCAM-1-specific antibodies to decrease adhesion of bone marrow cells to bone marrow stromal cells would be the interruption of progenitor/stroma binding.

An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction. This is not the same from introducing subject matter never present in the specification as filed where no apparent error existed. Obviousness is not the standard for addition new limitations to the disclosure as filed. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Adding information to the specification not supported by the disclosure as filed is considered new matter in that introduces new concepts violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action.

6. The specification is objected to and claims 30-33 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

As indicated above in section 5 in the new matter rejection, there is insufficient information or guidance as how to use VCAM-1-specific antibodies in "a method of interfering with interaction between a bone marrow stromal cells expressing VCAM-1 and a hemopoietic precursor cell which comprises administering an antibody to VCAM-1 in an amount effective to decrease VCAM-1-mediated adhesion between the bone marrow stromal cell and hemopoietic precursor cell".

As indicated above in section 5, Torok-Storb states that one of ordinary skill in the art after being informed of the discovery of VCAM-1 expression on bone marrow stromal cells and their involvement in mediating adhesive interactions between hemopoietic cells and stromal elements would have understood from the disclosure in the application that a clear therapeutic benefit of administering VCAM-1-specific antibodies to decrease adhesion of bone marrow cells to bone marrow stromal cells would be the interruption of progenitor/stroma binding.

However the specification as filed does not provide any guidance on how to use the VCAM-1 specific antibodies in this manner as described by Torok-Storb or any other manner as encompassed by the claimed methods. The specification is drawn to inhibiting lymphocyte adherence not hemopoietic stem and progenitor cell adherence. The disclosure does not provide direction or guidance as to which therapeutic conditions and what therapeutic endpoints are would be appropriate for the claimed methods.

Therefore, in addition to the new matter rejection set forth above,
The specification does not teach how to extrapolate data obtained from in vitro binding studies of marrow stromal elements to the development of effective in vivo therapeutic methods to interfere with hemopoietic cell-marrow stroma interactions, commensurate in scope with the claimed invention. Undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for interfering with inhibiting with hemopoietic cell-marrow stroma interactions in a therapeutic method.

7. Claims 30 and 32-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for VCAM-1-specific antibody 6G10 or antigen-binding specificities like 6G10 (Example 5) to bind marrow stromal elements does not reasonably provide enablement for any other VCAM-1-specific antibodies for the reasons of record set forth in the last Office Action (Paper No. 6) as they apply to the newly amended claims.

Applicant's arguments, filed 12/12/96 (Paper No. 23),have been fully considered but are not found convincing.

Applicant argues in conjunction with In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988) that it would not be undue experimentation to enable other VCAM-1-specific antibodies that bind to human marrow stromal cells. Applicant also likens the instant application to Example J of USPTO Traning Materials for Enablement (Fall, 1990). However for the reasons of record and those set below, the rejection is based upon limiting the scope to the particular VCAM-1 specificity and not to a particular VCAM-1-specific antibody. The rejection is based upon sound scientific reasoning and the evidence of record in the instant application. The

specification discloses that other VCAM-1-specific antibodies which recognize VCAM-1 on human endothelium do not bind significantly to human bone marrow stroma (Example 5). Therefore, the antigenic epitope recognized by the 6G10 antibody appears unique compared to other VCAM-1-specific antibodies. Applicant's claimed specificity is not consistent and commensurate in scope with applicant's own admission in the specification as-filed. Applicant is enabled only for the 6G10 antibody specificity to isolate or immunoselect of identify bone marrow stromal cells that express VCAM-1.

Applicant argues that Liesveld et al. (Blood, 1993) does show the VCAM-1-specific antibody 4B9 does bind to marrow stroma and was able to partially inhibit binding of a myeoblastic cell lines to marrow stroma some inhibition. However, Liesveld et al. discloses that VCAM-1-specific antibodies was not able to inhibit the adhesion of other cell types and in particular CD34+ cells (see entire document, page 116, column 2, Normal CD34+ progenitors). The claimed hemopoietic precursors are encompassed by these normal CD34+ progenitors.

Applicant argues that Simmons et al. (Blood, 1992) does teach the inhibition of hemopoietic cells adherence to marrow stromal elements. It is noted that such inhibition was performed under in vitro conditions wherein the VCAM-1 was induced to high levels with cytokines in contrast to the low levels of constitutive expression of VCAM-1 (see Abstract). Also, Simmons et al.states that is was significant that one was unable to completely block the binding of hemopoietic progenitors with VCAM-1-specific antibodies alone or in combination (Discussion).

In addition, Simmons et al., discloses that notably the molecular weight of the glycoproteins immunoprecipitated by 6G10 was 130 kD, some 20 kD larger than that of VCAM-1 expressed by endothelial cells of human and primate origin. This finding may reflect selective expression by bone marrow stroma of the recently identified VCAM-1 in a form that incorporates an additional seventh domain in its extracellular portion (page 393 (column 2, paragraph 2). Therefore, there is further evidence that the specificities associated with the 6G10 antibody for bone marrow stromal elements would not be expected with other VCAM-1-specific antibodies.

Applicant's arguments are not found persuasive as they apply to newly amended claims.

8. Similarly to what was pointed out in the last Office Action upon consideration of the art, applicant's instant claims drawn to methods of interfering with hemopoietic cell-marrow stroma interactions are free of the prior art. As disclosed in the instant specification (Example 5), known VCAM-1-specific antibodies at the time the invention was made did not bind to bone marrow stromal elements. Further, the prior art was directed towards the use of VCAM-1-specific antibodies in inhibiting inflammatory conditions and not towards inhibiting the interaction between bone marrow stromal cells and bone marrow hemopoietic cells.

9. No claim allowed.

10. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

11. This application is subject to the provisions of Public Law 103-465, effective June 8, 1995. Accordingly, since this application has been pending for at least two years as of June 8, 1995, taking into account any reference to an earlier filed application under 35 U.S.C. 120, 121 or 365(c), applicant, under 37 CFR 1.129(a), is entitled to have a first submission entered and considered on the merits if, prior to abandonment, the submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a first submission and the appropriate fee of $375 for a small entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

If applicant has filed multiple proposed amendments which, when entered, would conflict with one another, specific instructions for entry or non-entry of each such amendment should be provided upon payment of any fee under 37 CFR 1.17(r).

12. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4242 or (703) 305-7939.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
March 12, 1997

LILA FEISEE
SUPERVISORY PATENT EXAMINER
GROUP 1800